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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ROARK, JESSICA H	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/726,258	HSEI ET AL.	
	Examiner	Art Unit	
	Jessica H. Roark	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *2-4,6,7,9,20,22,23 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,8,10-19,21,24-26 and 28-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election of a conjugate consisting essentially of one or more Fab' fragments, attached to no more than about 10 nonproteinaceous molecules, which has a size of at least about 500kD and at least about 8 fold greater than the apparent size of at least one antibody fragment, wherein the nonproteinaceous molecule is a single chain PEG of at least about 20kD in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

In order to facilitate the prosecution of this application, applicant is requested to consider inserting a claim drawn solely to the above elected species and canceling all non-elected embodiments from the claims.

Claims 2-4, 6-7, 9, 20, 22-23 and 27 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected species.

Claims 1, 5, 8, 10-19, 21, 24-26 and 28-35 *are under consideration in the instant application.*

2. Each of provisional applications 60/074,330; 60/094,013; 60/094,003; and 60/075,467 appears to provide adequate written support for the instant claims. Thus the instant claims are considered to have an effective filing date of 1/22/98.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

It is suggested that Applicant amend the title to -- ANTIBODY FRAGMENT-PEG CONJUGATES --.

4. The formal drawings submitted 5/31/01 have been approved by the Draftsman.

Applicant is reminded to amend the Brief Description of the Drawings to correspond to the approved formal drawings. For example, Figure 48 is listed as consisting of 48A-48T on page 12 at line 17, whereas the formal drawings actually provide Figures 48A-48Z.

Appropriate correction is required.

5. Applicant's IDS, filed 11/29/00 (Paper No. 5), is acknowledged.

However, the references cited on the PTO-1449 were not available to the Examiner for consideration. The Examiner has supplied the referenced U.S. Patents and the WO documents listed on the submitted forms PTO-1449 and considered them, as indicated on the attached copies, along with certain of the non-patent literature references.

Applicant is invited to re-supply the missing non-patent references so that they may be considered.

6. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

Applicant is reminded that the current address of the ATCC is:
American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209.

The references to the ATCC address at least on page 188 at lines 3 and lines 14 should be corrected accordingly. Applicant is requested to review the specification to determine if the incorrect address occurs elsewhere.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 5, 8, 10-19, 21, 24-26 and 28-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 5, 8, 10-19, 21, 24-26 and 28-35 are indefinite in reciting "consisting essentially of" because it is not clear what elements are encompassed that would not affect the basic characteristics of the recited compound. "Consisting essentially of" is considered indefinite when used with a compound rather than a composition.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

9. It is noted that the specification on page 25 at lines 13-22 defines the term "apparent size" as limited to the size of a molecule as determined using size exclusion chromatography and comparing to a standard curve produced using globular protein molecular weight standards.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1, 5, 8, 10-19, 21, 26 and 28-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a conjugate consisting of an art-recognized antibody fragment such as an Fab' covalently attached to a specific number of PEG molecules depending upon the number and distribution of sites available, does not reasonably provide enablement for a conjugate of any antibody fragment covalently coupled to any nonproteinaceous polymer or "no more than 10 nonproteinaceous polymer molecules". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not appear to provide a sufficiently enabling description of the instant invention. In particular, the specification does not appear to provide sufficient guidance regarding how to produce conjugates as broadly defined by the claims. The claims are broadly drawn to a conjugate consisting of *any* antibody fragment wherein the antibody fragment is covalently attached to *any* nonproteinaceous polymer molecule.

The claims broadly encompass a conjugate comprising an antibody fragment as small as a single amino acid residue. However, the specification does not appear to have provided sufficient guidance as to how the skilled artisan would make and use conjugates comprising antibody fragments other than art-recognized fragments such as the Fab, Fab', Fab'-SH, Fv, scFv and $F(ab')_2$ fragments of an antibody. There does not appear to be sufficient guidance in the specification as filed for the myriad "fragments" which are encompassed within the instant claim language. One of skill in the art would neither expect nor predict the appropriate functioning of a conjugate consisting of an antibody fragment as broadly as now claimed.

In addition, the claims also encompass *any* nonproteinaceous polymer covalently coupled to an antibody, which includes such diverse molecules as DNA, plastics, liposomes and so forth (see page 75 of the instant specification). The specification discloses covalent coupling of the nonproteinaceous polymer PEG to an antibody and Fab', Fab-SH and $F(ab')_2$ of an antibody (e.g., see pages 216-226) via the known chemistries on page 76 of the specification. However, the specification does not appear to provide sufficient guidance as to how to covalently couple a sufficient number of other types of nonproteinaceous polymers to the antibody or antibody fragments. This it would require undue experimentation of the skilled artisan to make and use these other "nonproteinaceous polymer" conjugates.

Finally, although several conjugates of antibodies and antibody fragments to PEG are disclosed in the specification (e.g., the conjugation of a single PEG to the free thiol of the unpaired cysteine at the COOH terminus of the Fab' fragment, as disclosed on pages 216-220 of the specification); the instant claims provide insufficient limitations in terms of number and placement of the covalent attachments that link any particular antibody fragment to a particular number of PEG molecules.

In particular, the instant claims require that the recited Fab' fragment be covalently attached *to no more than 10 nonproteinaceous molecules*. The expression vector disclosed in the specification for use in producing an Fab' fragment is derived from human IgG1 and has a free cysteine at the carboxy terminus of the heavy chain (see page 216). As disclosed in the example on pages 216 to 220, it is this cysteine at the carboxy terminus of the Fab' fragment that was used in the working example of pages 216-220 of the specification to couple a single PEG molecule to the Fab' of interest. The human IgG1 Fab' structure permits coupling of a single PEG because only the cysteine at the carboxy terminus is available for the coupling reaction - the other cysteines present in the heavy and light chain components of the Fab' fragment are involved in either intrachain or interchain disulfide bridges (e.g., see the schematic representation of the five classes of human immunoglobulins in Figure 14 of Chapter 9 of "Fundamental Immunology", Second Edition, W.E. Paul editor, Raven Press Ltd., New York, 1989, page 225).

Thus the skilled artisan would not reasonably expect that an unmodified Fab' molecule could be covalently coupled via the methods disclosed in the specification to more than one PEG molecule.

Consequently, only in the case of claims 24-25 does there appear to be a clearly enabled embodiment of an antibody fragment that is an Fab, Fab' or Fab'-SH covalently attached to no more than one PEG molecule. Thus for the elected species of an Fab' fragment coupled to a nonproteinaceous molecule that is a PEG, it appears that the instantly elected number of nonproteinaceous molecules attached must be one.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, it would be unpredictable as to which of the myriad "fragments" and "nonproteinaceous polymers" encompassed by the instant claims could be used in what combinations of numbers of linkages to produce the instant conjugate; thus the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue.

12. The following art rejections under 35 USC 102(e) are set forth with respect to the elected species of an Fab' antibody fragment covalently attached to no more than about 10 PEG molecules, wherein the PEG is single chain PEG having an average molecular weight of at least about 20 kD, as limited to the enabled embodiment with respect to the number of PEG molecules linked to a particular antibody fragment.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in-

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

14. Claims 1, 5, 8, 10-19, 21, 24-26 and 28-35 are rejected under 35 U.S.C. 102(e) as being anticipated by Gonzalez et a. (U.S. Patent No. 6,133,426, see entire document).

Gonzales et al. teach a conjugate comprising an antibody Fab' (Fab'-SH) covalently attached to a single PEG molecule, wherein the PEG has an average molecular weight of at least about 20kD (see especially example T at columns 121-123) Gonzales et al. also teach that the conjugate of an antibody Fab' fragment and a single PEG is a conjugate that has an apparent size of at least about 500 KD (see Figure 60 for the 20 kD conjugate) and that this is at least about 8 fold greater than the apparent size of the antibody fragment of 59 kD (see especially column 123 at lines 14-34). With respect to the unmutated Fab' fragment, the PEG is taught to be attached at the free Cys of the hinge region (see e.g., column 121 at lines 1-21).

Gonzalez et al. also teach that the PEG can be attached to a cysteine residue in the light or heavy chain of the antibody fragment that would ordinarily form the disulfide bridge linking the light and heavy chains, wherein the disulfide bridge is avoided by substituting another amino acid , such as serine, for the corresponding cysteine residue in the opposite chain (e.g., column 24 especially lines 46-58).

Gonzales et al. also teach that the Fab' can comprise a humanized anti-human IL-8 antigen binding site, including the complementarity determining regions of a light chain polypeptide amino acid sequence that is either 6G4V11N35A or 6G4V11N35E (e.g., columns 15 at lines 52-67, column 16 at lines 1-6, column 74 at lines 18-26, and claims).

Gonzales et al. also discloses conjugates further comprising avidin or biotin, i.e., nonproteinaceous label molecules (e.g., column 84 especially lines 9-19) or radiolabels (e.g., column 96 especially lines 20-31). Instant claims 33 and 34 are included in this rejection because Gonzalez et al. teach that, unless specifically indicated to the contrary, "conjugate" is defined as a heterogeneous molecule formed by the covalent attachment of one or more antibody fragment(s) to one or more polymer molecule(s) (especially column 12 at lines 56-60), i.e., it is an inherent property of the conjugate that its covalent structure is free of any matter other than the antibody fragment(s) and the polymer, i.e., PEG, molecule(s).

The reference teachings anticipate the claimed invention.

15. Claims 1, 5, 8, 10-19, 21, 24-26 and 28-35 are rejected under 35 U.S.C. 102(e) as being anticipated by Gonzalez et a. (U.S. Patent No. 6,025,158, see entire document).

Gonzales et al. teach a conjugate comprising an antibody Fab' (Fab'-SH) covalently attached to a single PEG molecule, wherein the PEG has an average molecular weight of at least about 20kD (see especially example T at columns 120-123) Gonzales et al. also teach that the conjugate of an antibody Fab' fragment and a single PEG is a conjugate that has an apparent size of at least about 500 KD (see Figure 60 for the 20 kD conjugate) and that this is at least about 8 fold greater than the apparent size of the antibody fragment of 59 kD (see especially column 122 at lines 31-54). With respect to the unmutated Fab' fragment, the PEG is taught to be attached at the free Cys of the hinge region (see e.g., column 120 at lines 15-37).

Gonzalez et al. also teach that the PEG can be attached to a cysteine residue in the light or heavy chain of the antibody fragment that would ordinarily form the disulfide bridge linking the light and heavy chains, wherein the disulfide bridge is avoided by substituting another amino acid , such as serine, for the corresponding cysteine residue in the opposite chain (e.g., column 25 especially lines 31-54).

Gonzales et al. also teach that the Fab' can comprise a humanized anti-human IL-8 antigen binding site, including the complementarity determining regions of a light chain polypeptide amino acid sequence that is either 6G4V11N35A or 6G4V11N35E (e.g., column 15 especially lines 42-65, columns 98-120, especially columns 113-120, and claims).

Gonzales et al. also discloses conjugates further comprising avidin or biotin, i.e., nonproteinaceous label molecules (e.g., column 83 at lines 48-58) or radiolabels (e.g., columns 95-96, especially column 95 at lines 55-67). Instant claims 33 and 34 are included in this rejection because Gonzalez et al. teach that, unless specifically indicated to the contrary, "conjugate" is defined as a heterogeneous molecule formed by the covalent attachment of one or more antibody fragment(s) to one or more polymer molecule(s) (especially column 12 at lines 53-65), i.e., it is an inherent property of the conjugate that its covalent structure is free of any matter other than the antibody fragment(s) and the polymer, i.e., PEG, molecule(s).

The reference teachings anticipate the claimed invention.

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1, 5, 8, 10-13, 15-19, 21, 24-25, 30-33 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zapata et al. (FASEB J. 1995, Abstract #1288, 9:A1479, IDS # 98) in view of Braxton (US Pat. No. 5,766,897, IDS #20).

The claims are drawn to antibody Fab' fragments conjugated to single chain PEG of at least about 20 kD.

Zapata et al. teach a conjugate consisting essentially of a humanized anti-CD18 Fab' fragment covalently coupled via a sulfhydral group in the hinge region to a single chain PEG molecule (MePEG) that is either 5 kD or 10kD (see entire Abstract). Zapata et al. also teach that the Fab' fragment coupled to either size PEG did not interfere with the ability of the antibody to bind CD18, and reduced the clearance rate relative tot the native Fab' molecule (Abstract middle). Zapata et al. note that the ability to extend the clearance rate of an antibody Fab' fragment without affecting antigen binding increased significantly the potential therapeutic value of the antibody (concluding remark).

Zapata et al. do not teach a conjugate in which the PEG is single chain molecule of at least about 20 kD.

However, Zapata et al. also note that although both the 5 kD and 10 kD forms of PEG reduced serum clearance, the 10 kD form of PEG was better than the 5 kD form (see last third of Abstract). Consequently, Zapata et al. clearly recognize that increasing the size of the PEG resulted in a further reduction the clearance rate. Thus the teaching of Zapata et al. establish that the size of the PEG molecule was a variable that affected the desirable property of reducing serum clearance rates, with a larger size producing a better effect.

Thus it would have been obvious to one of ordinary skill in the art to use higher molecular weight PEGs for covalent linkage to any Fab' antibody fragment for which one desired to reduce the serum clearance rate.

In addition, Braxton teach methods for the PEGylation of proteins by attaching a PEG molecule via the thiol group on a free cysteine (see entire document, e.g., column 12 especially lines 48-50). Braxton teach that the molecular weight of the attached PEG may be from 200 to 20,000 MW (i.e., from about 0.2 to 20 kD) and that particularly for relatively small proteins that generally have short half lives and because of their small size have fewer PEG sites available, the PEG moiety used should be of a higher molecular weight (see especially lines 48-65). Since Braxton does not stipulate that the PEG is a branched chain polymer, the PEG taught by Braxton is also a single chain molecule. Braxton also teaches formulation of the PEGylated proteins in a pharmaceutical composition comprising a carrier (e.g., columns 24-28). Although it is not explicitly stated that the pharmaceutical composition was sterile, sterility is requisite for therapeutics and so would have been obvious to one of ordinary skill in the art at the time the invention was made.

Given the guidance provided by Braxton higher molecular weight PEGs should be used when only a few coupling sites are available on relatively small proteins, and the identification by Braxton of 20 kD as being the upper end of the molecular weight range of PEGs taught; it would have been obvious to the ordinary artisan at the time the invention was made to select a 20 kD PEG for use in coupling to relatively small proteins, including the Fab' antibody fragments as taught by Zapata et al. Given the simple substitution of a higher molecular weight PEG, the ordinary artisan at the time the invention was made would have had a reasonable expectation of producing a humanized anti-CD18 Fab' fragment covalently coupled to a single 20 kD single chain PEG. Given the teachings of Zapata et al., particular in view of the teachings of Braxton, the ordinary artisan would have been motivated to formulate such a conjugate in order to further reduce the serum clearance of a therapeutic antibody. Although the references are silent with respect to the apparent size of the conjugate and the relationship of the apparent size of the conjugate to that of the unconjugated Fab' fragment; given that the same product is produced (an Fab' fragment coupled to a 20 kD single chain PEG), that product would necessarily have an apparent size of at least about 500 kD and that would be at least about 8 fold greater than the apparent size of at least one antibody fragment. Further, one of ordinary skill in the art at the time the invention was made would have been motivated to produce a conjugate, wherein the covalent structure of said conjugate was free of any matter other than the antibody fragment and the nonproteinaceous polymer to insure purity, potency and sterility of the conjugate for therapeutic use. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. Claims 26 and 28 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zapata et al. (FASEB J. 1995, Abstract #1288, 9:A1479, IDS # 98) in view of Braxton (US Pat. No. 5,766,897, IDS #20) as applied to claims 1, 5, 8, 10-13, 15-19, 21, 24-25, 30-33 above, and further in view of Doerschuk et al (U.S. Patent No. 5,702,946, IDS #18).

The claims are drawn to anti-IL-8 and humanized anti-IL-8 Fab' fragments conjugated to single chain PEG of at least about 20 kD.

Zapata et al. in view of Braxton have been discussed supra.

Zapata et al. in view of Braxton do not teach that an antibody Fab' fragment that binds to human IL-8.

Doerschuk et al. teach anti-IL-8 monoclonal antibodies and Fab' fragments of these antibodies, as well as humanized anti-IL-8 antibodies and humanized anti-IL-8 Fab' fragments (see entire document, e.g. columns 1-2 and claims). Doerschuk et al. also teach the use of the anti-IL-8 antibody and humanized antibody fragments for treatment and diagnosis of inflammatory disorders (e.g., columns 13-14). Thus Doerschuk et al. establish that anti-IL-8 antibodies, including humanized anti-IL-8 antibodies are therapeutically and diagnostically valuable.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention by substituting the anti-IL-8 Fab' fragments of Doerschuk et al. for the anti-CD18 Fab' conjugate taught by Zapata et al. in view of Braxton. One of ordinary skill in the art would have been motivated to add PEG to an anti-IL-8 Fab' fragment using the method of Zapata et al. and Braxton because Doerschuk et al. teach the usefulness of anti-IL-8 monoclonal antibody Fab' fragments in treatment and diagnosis of inflammatory disorders and because both Zapata et al. and Braxton teach that addition of PEG reduces serum clearance of therapeutics and reduces immunogenicity. Given the availability of the anti-IL-8 Fab' fragment and the methods of adding PEG, including a 20kD single chain PEG to an antibody Fab' fragment, the ordinary artisan at the time the invention was made would have had a reasonable expectation of producing the instant invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. Claims 34 and 35 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zapata et al. (FASEB J. 1995, Abstract #1288, 9:A1479, IDS # 98) in view of Braxton (US Pat. No. 5,766,897, IDS #20) as applied to claims 1, 5, 8, 10-13, 15-19, 21, 24-25, 30-33 above, and further in view of Griffiths et al (U.S. Patent No. 5,670,132, IDS #13).

The claims are drawn to Fab' fragments conjugated to single chain PEG of at least about 20 kD and incorporating into the covalent structure of the conjugate one or more radiolabels.

Zapata et al. in view of Braxton have been discussed supra.

Zapata et al. in view of Braxton do not teach antibody fragment-PEG conjugates that are radiolabeled.

Griffiths et al. teach a radiolabeled Fab'-PEG conjugate which includes in the covalent structure of the conjugate a radiolabel (see entire document, e.g., Abstract). Griffiths et al. also teach the use of the radiolabeled conjugate in in vivo diagnostics (see column 1, last paragraph and column 2, last paragraph and continuing onto column 3). Griffiths et al. teach that coupling of PEG to Fab' fragments is desirable because addition of PEG to an Fab' avoids the accumulation of Fab' fragments in the kidney and thereby improves the use of Fab' fragments in in vivo diagnostics (e.g., column 1, especially lines 46-60), in addition to an art recognized benefit of reducing the rate of serum clearance (e.g., column 1 especially lines 52-54),. Griffiths et al. also teach conjugates that are to be administered internally to a patient (other than oral administration) are stored under sterile conditions and administered in sterile pharmaceutically acceptable carriers (especially column 5, lines 45-61).

It would therefore have been obvious to one of ordinary skill in the art at the time the invention was made to label the Fab'-PEG 20 kD conjugate as taught by Zapata et al. and Braxton, with a radiolabel as taught by Griffiths et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in light of Griffiths teaching that the addition of a radiolabel permits in vivo diagnostic use of antibody Fab' fragments; and in view of the teachings of Zapata et al. and Braxton with respect to the reduced serum clearance of 20kD PEG compared to the smaller 5 kD PEG exemplified by Griffiths et al. One of ordinary skill in the art at the time the invention was made would have been motivated to produce a conjugate, wherein the covalent structure of said conjugate was free of any matter other than the antibody fragment, the nonproteinaceous polymer and the label molecule to insure purity and potency of the conjugate for in vivo diagnostic use. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 1, 5, 8, 10-19, 21, 24-26 and 28-35 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 10-13, 15-19, 21, 24-26 and 28-34 of copending Application No. USSN 09/355,014. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '014 application recite all the limitations recited in the instant claims, indicating that the limitations set forth in the instant claims were obvious embodiments of the invention claimed in USSN 09/355,014.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

22. Claims 1, 5, 8, 10-19, 21, 24-26 and 28-35 are directed to an invention not patentably distinct from claims 1, 5, 10-13, 15-19, 21, 24-26 and 28-34 of commonly assigned USSN 09/355,014 for the reasons set forth supra.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned USSN 09/489,394, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

23. No claim is allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
June 28, 2002

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TECH CENTER 1600
6/28/02